Reaction of 3-Hydroxy-1,2,3,4-tetrahydroquinoline-2,4-diones with Ethyl(Triphenylphosphoranylidene)acetate

Stanislav Kafka, Michal Kovář, and Antonín Klásek*

Department of Chemistry and Environmental Technology, Faculty of Technology, Technical University of Brno, 762 72 Zlín, Czech Republic

Thomas Kappe

Institut für Organische Chemie, Karl-Franzens Universität, A-8010 Graz, Austria

Dedicated to Professor Miha Tišler on the occasion of his 70th birthday

The Wittig reaction of 3-hydroxy-1,2,3,4-tetrahydroquinoline-2,4-diones **2** with ethyl (triphenylphosphoranylidene)acetate **3** proceeds stereoselectively to give *E*-4-carbethoxymethylene-1,2,3,4-tetrahydro-2-quinolones **4**, which were hydrolyzed to corresponding acids **6**. Butenolides **5** were detected and, in some cases, isolated as a minor product of the Wittig reaction.

J. Heterocyclic Chem., **33**, 1977 (1996).

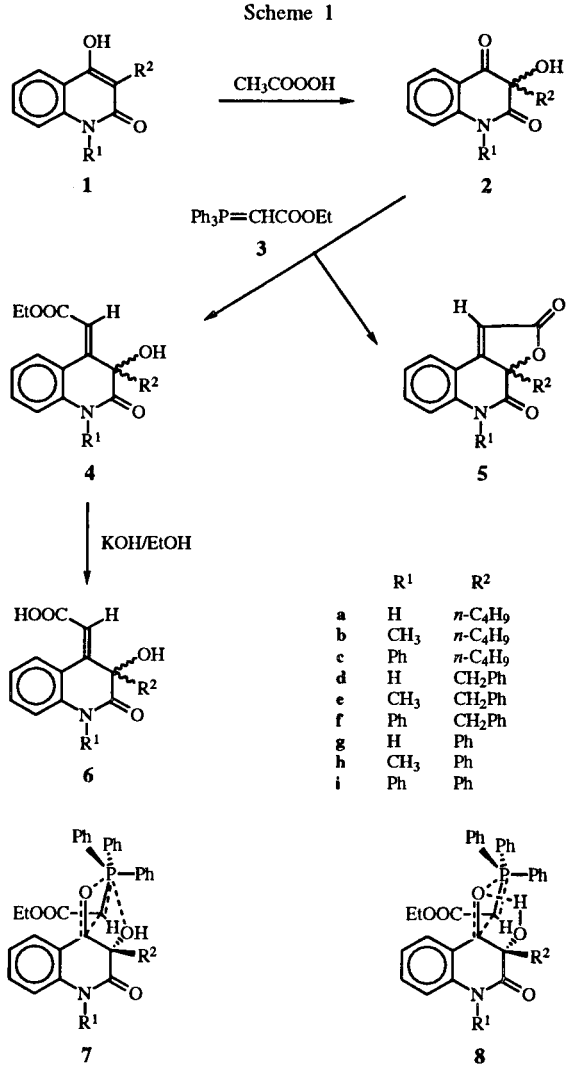
Many arylacetic and arylpropionic acids (including heteroaryl derivatives) are known as antiinflammatory agents. Also γ-lactones attached to an aromatic ring system exhibit strong antiinflammatory activity [1]. In the 2-quinolone series, some γ- and δ-lactones were prepared [2] from esters arising by the Wittig reaction of quinisatine or its *N*-methylderivative with ethyl (triphenylphosphoranylidene)acetate. This reaction proceeds smoothly and only the 3-oxo group is attacked by the Wittig reagent.

It is known [3] that α-hydroxy ketones react with ethyl (triphenylphosphoranylidene)acetate **3** to give *E*-4-hydroxy-2-alkenoates. Therefore, the suitable substrates for the Wittig reaction in quinoline series are 3-hydroxy-1,2,3,4-tetrahydroquinoline-2,4-diones **2**, known as metabolites of some *Pseudomonas* species [4,5]. These compounds are available from 4-hydroxy-2(1*H*)-quinolones **1** by their photooxidation [6] or oxidation with peroxy acids [4,7], or by the reaction of quinisatines and/or their hydrates and aminales with phenols [8,9].

In this paper we describe the reaction of 3-hydroxy-1,2,3,4-tetrahydroquinoline-2,4-diones **2** with ethyl (triphenylphosphoranylidene)acetate **3**. The Wittig syntheses and the consecutive hydrolysis of the products are depicted in Scheme 1.

The reactions of **2** with stabilized ylid **3** proceed stereoselectively in accord with Ref [3] and the main (in some cases single) isolated products were *E*-4-ethoxycarbonylmethylene-1,2,3,4-tetrahydro-2-quinolones **4**. To the best of our knowledge, 2-quinolones with the exocyclic double bond in the position 4 were not described until now. In the ^{1}H nmr spectra of esters **4**, the well distinguishable ABCD system of aromatic protons is present and, in most cases, the assignment of these protons is possible without any problems. The isolated singlet in the range of approximately 5.8-6.8 ppm belong to the olefinic proton of exocyclic double bond and its position is strongly influenced by the character of the substituents at 3-C and at the nitrogen atom. The *cis*-orientation of this olefinic proton and OH group at 3-C in the compound **4e** was confirmed by nOe experiments. In the ^{1}H nmr spectra of *N*-phenyl derivatives **4c**, **4f** and **4i**, the remarkable upfield

Scheme 1



	R^1	R^2
a	H	*n*-C_4H_9
b	CH_3	*n*-C_4H_9
c	Ph	*n*-C_4H_9
d	H	CH_2Ph
e	CH_3	CH_2Ph
f	Ph	CH_2Ph
g	H	Ph
h	CH_3	Ph
i	Ph	Ph

Table 1

Physical and Analytical Data of Compounds 2

Compound No.	R^1	R^2	Yield (%)	Mp (°C) (Solvent)	Formula	Analysis (%) Calcd./Found C	H	N
2a	H	n-C_4H_9	80	146-9 (benzene)	$C_{13}H_{15}NO_3$ 233.3	66.94 66.76	6.48 6.56	6.00 5.78
2b	CH_3	n-C_4H_9	83	104-8 (cyclohexane)	$C_{14}H_{17}NO_3$ 247.3	68.00 67.90	6.93 7.11	5.66 5.59
2c	C_6H_5	n-C_4H_9	59	122-5 (benzene)	$C_{19}H_{19}NO_3$ 309.4	73.77 73.65	6.19 6.23	4.53 4.50
2d	H	$C_6H_5CH_2$	86	205-7 (ethanol)	[7]			
2e	CH_3	$C_6H_5CH_2$	84	131-3 (benzene)	[6]			
2f	C_6H_5	$C_6H_5CH_2$	66	165-6 (benzene)	[6]			
2g	H	C_6H_5	92	234-5	[6]			
2h	CH_3	C_6H_5	86	158-61	[7]			
2i	C_6H_5	C_6H_5	93	166-7 (benzene)	[7]			

doublet (approximately 6.2-6.6 ppm) of one aromatic proton is present. This doublet appears also in the nmr spectra of *N*-phenyl derivative of starting substance **2c** and it was earlier assigned [6] to an *o*-anilino proton. But, on the basis of the COSY experiment, the upfield resonating proton appertains to H-8, which is shielded by circular current of π-electrons of the *N*-phenyl group in an equatorial position of the ring B. With a COSY experiment (in the case of compound **4c**), the long-range couplings ^5J of olefinic proton to OCH_2 group and to 5-H were also discovered. In the ^{13}C nmr spectrum of **4c**, *N*-phenyl *ortho*- and *meta*-carbons are broadened; that might be an effect of quadrupolar nitrogen or some exchange process (hindered rotation, for example) but no true magnetic nonequivalence was observed. The ir spectra of the esters **4** are in accordance with their structure. Characteristic absorption bands occured at 3390-3500 cm^{-1} (sharp, associated OH), 3280-3320 cm^{-1} (broad, associated NH), 1632-1642 cm^{-1} (lactam), 1700-1730 cm^{-1} (unsaturated ester) and 1599-1605 cm^{-1} (double bonds).

The formation of *E*-isomers **4** may be rather surprising, because, in consequence of the strong steric interaction of hydrogen atom at C-5 with ethoxycarbonyl group, the coplanarity of the exocyclic double bond with benzene ring is excluded. More thermodynamically stable is the appropriate *Z*-isomer (or its lactone **5**, respectively), in which the coplanarity of the system ethoxycarbonyl group - carbon-carbon double bond - benzene ring is possible. But, for the stereochemistry of the product, the differences in steric interactions of the transition states are decisive [3,10].

Two transition-state models of the hydroxyl-directed Wittig reaction were proposed [3]. The first of them assumes initial interaction of the α-hydroxyl group with the phosphorus atom of the ylide **3** followed by the formation of a bicyclic transition state **7**, in which the equatorial position of a carbethoxy group at the five-membered ring is preferred. The formula **8** represents the second model which assumes the activation of the carbonyl group by an intramolecular hydrogen bond and following cycloaddition of the ylide **3**. This model is characterized with the sterically more advantageous opposite orientation of carbethoxy group to the substituents in the position 3 of the quinoline system. Both presented transition states **7** and **8** are in accordance with the requirement of the coplanarity of the carbethoxy group and the incipient carbon-carbon double bond necessary for the overlap between their π-orbitals [10] and both lead (after *syn*-elimination of triphenylphosphane oxide) to the formation of the isolated *E*-isomers **4**. In our opinion, the transition state **8** is more probable due to smaller steric interactions between bulky substituent at C-3 and phenyl groups at phosphorus atom.

The minor products **5a-d**, **5f** and **5i** were isolated by column chromatography of the crude products from the reactions of appropriate compounds **2** with the ylid **3**. These butenolides showed a characteristic light blue fluorescence at 254 and also at 366 nm and were detected by tlc in all crude products of the reactions of **2** with **3**. Their nmr spectra are generally in accordance with those of esters **4**; the signals of olefinic protons are shifted downfield or upfield if the spectra were measured in hexadeuteriodimethylsulfoxide or deuteriochloroform, respectively. In the ir spectra of the butenolides **5**, characteristic absorption bands appear at 1630-1640 cm^{-1} (lactam) and 1599-1605 cm^{-1} (double bonds); in the connection with the magnification of the strain as compared with esters **4**, the absorption bands of lactone carbonyls are shifted to 1740-1780 cm^{-1}.

Butenolides **5** can arise by the conversion of a less sterically advantageous transition state with the *cis*-arrangement of carbethoxy and hydroxyl groups (contrary to the formulas

Table 2

Physical and Analytical Data of Compounds **4** and **6**

Compound No.	R^1	R^2	Method Yield (%)	Mp (°C) (Solvent)	Formula	Analysis (%) Calcd./Found C	H	N
4a	H	n-C_4H_9	B: 72	131-133 (benzene)	$C_{17}H_{21}NO_4$	67.31 67.27	6.98 7.21	4.62 4.61
4b	CH_3	n-C_4H_9	B: 83	59-61 (cyclohexane)	$C_{18}H_{23}NO_4$	68.12 68.01	7.30 7.48	4.41 4.37
4c	C_6H_5	n-C_4H_9	A: 95	52-58 (ethanol)	$C_{23}H_{25}NO_4$	72.80 72.72	6.64 6.66	3.69 3.65
4d	H	$C_6H_5CH_2$	A: 69 B: 64	187-189 (ethanol)	$C_{20}H_{19}NO_4$	71.20 71.41	5.68 5.73	4.15 4.02
4e	CH_3	$C_6H_5CH_2$	A: 73 B: 78	130-131 (benzene)	$C_{21}H_{21}NO_4$	71.78 71.92	6.02 6.18	3.99 3.91
4f	C_6H_5	$C_6H_5CH_2$	B: 85	186-190 (benzene)	$C_{26}H_{23}NO_4$	75.53 75.45	5.61 5.73	3.39 3.45
4g	H	C_6H_5	B: 65	211-213 (benzene)	$C_{19}H_{17}NO_4$	70.58 70.09	5.30 5.46	4.33 4.40
4h	CH_3	C_6H_5	A: 57 B: 67	131-134 (benzene)	$C_{20}H_{19}NO_4$	71.20 71.07	5.68 5.87	4.15 4.14
4i	C_6H_5	C_6H_5	A: 48 B: 50	135-136 (benzene)	$C_{25}H_{21}NO_4$	75.17 75.02	5.30 5.43	3.50 3.42
6a	H	n-C_4H_9	97	202-204 (benzene)	$C_{15}H_{17}NO_4$	65.44 65.21	6.22 6.32	5.09 4.97
6b	CH_3	n-C_4H_9	87	153-155 (benzene)	$C_{16}H_{19}NO_4$	66.42 66.27	6.62 6.75	4.84 4.76
6c	C_6H_5	n-C_4H_9	70	166-167 (acetic acid)	$C_{11}H_{21}NO_4$	71.78 71.39	6.02 6.23	3.99 3.85
6d	H	$C_6H_5CH_2$	86	211-213 (acetic acid)	$C_{18}H_{15}NO_4$	69.89 69.90	4.89 4.99	4.53 4.49
6e	CH_3	$C_6H_5CH_2$	82	197-200 (benzene)	$C_{19}H_{17}NO_4$	70.58 70.41	5.30 5.42	4.33 4.35
6f	C_6H_5	$C_6H_5CH_2$	97	154-155 (acetic acid)	$C_{24}H_{19}NO_4$	74.79 74.43	4.97 5.13	3.63 3.57
6g	H	C_6H_5	85	227-228 (methanol)	$C_{17}H_{13}NO_4$	69.15 69.01	4.44 4.67	4.74 4.50
6h	CH_3	C_6H_5	98	248-250 (acetic acid)	$C_{18}H_{15}NO_4$	69.89 69.58	4.89 5.01	4.53 4.39
6i	C_6H_5	C_6H_5	89	151-152 (benzene)	$C_{23}H_{17}NO_4$	74.38 74.12	4.61 4.87	3.77 3.54

7 and/or **8**). But, they may arise also in the course of the Wittig reaction by the isomerization of the product **4** to the *Z*-isomer and its following lactonization to thermodynamically more stable butenolide **5**, in which the steric hindrance of the coplanarity of the benzene ring with the carbon-carbon double bond is not present.

We have observed that even chromatographically pure esters **5** yields on thin-layer chromatograms an additional

Table 3

Physical and Analytical Data of Compounds **5**

Compound No.	R^1	R^2	Yield (%)	Mp (°C) (Solvent)	Formula	Analysis (%) Calcd./Found C	H	N
5a	H	n-C_4H_9	0.4	220-223 (ethanol)	$C_{15}H_{15}NO_3$	70.02 69.66	5.88 6.03	5.44 5.27
5b	CH_3	n-C_4H_9	2.2	206-209 (benzene)	$C_{16}H_{17}NO_3$	70.83 70.57	6.32 6.66	5.16 5.09
5c	C_6H_5	n-C_4H_9	4.2	213-216	$C_{21}H_{19}NO_3$	75.66 75.24	5.74 5.86	4.20 4.15
5d	H	$C_6H_5CH_2$	0.2	295-298	$C_{18}H_{13}NO_3$	74.22 74.12	4.50 4.72	4.81 4.76
5f	C_6H_5	$C_6H_5CH_2$	3.5	246-250 (benzene)	$C_{24}H_{17}NO_3$	78.46 78.31	4.66 4.82	3.81 3.75
5i	C_6H_5	C_6H_5	5.5	230-232	$C_{23}H_{15}NO_3$	78.17 77.97	4.28 4.41	3.96 3.85

Table 4

Spectroscopic Data of Compounds **2, 4, 5** and **6**

Compound No.	IR (cm^{-1})	^{1}H-NMR δ (ppm)
2a	3390-3460, 3180-3280, 1708, 1677, 1613, 1595, 1485, 1365, 1237, 1180, 1172, 1084, 758, 681	0.78 (t, J = 7 Hz, 3H, CH_3), 1.10-1.30 (m, 4H, H-2 and H-3 of butyl), 1.62-1.80 (m, 2H, H-1 of butyl), 5.67 (*s*, 1H, OH), 7.08 (d, J = 7 Hz, 1H, H-8), 7.13 (t, J = 7 Hz, 1H, H-6), 7.63 (dt, J = 7 and 2 Hz, 1H, H-7), 7.74 (dd, J = 7 and 2 Hz, 1H, H-5), 10.77 (s, 1H, NH)
2b	3460, 2941, 2862, 1699, 1657, 1602, 1582, 1472, 1457, 1414, 1296, 1218, 1188, 1105, 1079, 1029, 1018, 781, 768, 668	0.77 (t, J = 7 Hz, 3H, CH_3 of butyl), 1.08-1.24 (m, 4H, H-2 and H-3 of butyl), 1.63-1.78 (m, 2H, H-1 of butyl), 3.38 (*s*, 3H, NCH_3), 5.74 (*s*, 1H, OH), 7.24 (t, J = 7 Hz, 1H, H-6), 7.37 (d, J = 7 Hz, 1H, H-8), 7.74 (dt, J = 7 and 2 Hz, 1H, H-7), 7.82 (dd, J = 7 and 2 Hz, 1H, H-5)
2c	3340, 2958, 1721, 1684, 1604, 1491, 1465, 1350, 1320, 1299, 1172, 762, 709, 680, 666	0.80 (t, J = 7 Hz, 3H, CH_3), 1.10-1.40 (m, 4H, H-2 and H-3 of butyl), 1.80-2.00 (m, 2H, H-1 of butyl), 5.84 (s, 1H, OH), 6.35 (d, J = 8 Hz, 1H, H-8), 7.20 (t, J = 8 Hz, 1H, H-6), 7.20-7.70 (m, 6H, H-7 and C_6H_5), 7.86 (d, J = 8 Hz, 1H, H-5)
4a	3442, 3295, 2956, 1704, 1685, 1632, 1612, 1478, 1378, 1324, 1288, 1214, 1175, 1158, 1062, 1038, 1021, 865, 767	0.74 (t, J = 7 Hz, 3H, CH_3 of butyl), 1.05-1.25 (m, 4H, H-2 and H-3 of butyl), 1.18 (t, J = 7 Hz, 3H, CH_3 of ethyl), 1.35-1.57 (m, 2H, H-1 of butyl), 4.12 (q, J = 7 Hz, 1H, CH_2 of ethyl), 5.76 (*s*, 1H, OH), 6.28 (s, 1H, olef H), 6.93 (dd, J = 8 and 2 Hz, 1H, H-8), 6.98 (dt, J = 8 and 2 Hz, 1H, H-6), 7.33 (dt, J = 8 and 2 Hz, 1H, H-7), 7.46 (dd, J = 8 and 2 Hz, 1H, H-5), 10.47 (s, 1H, NH)
4b	3395, 2952, 2922, 2868, 1720, 1656, 1631, 1600, 1471, 1350, 1295, 1242, 1208, 1172, 1108, 1088, 1065, 1028, 767, 754	In deuteriochloroform: 0.77 (t, J = 7 Hz, 3H, CH_3 of butyl), 1.03-1.36 (m, 4H, H-2 and H-3 of butyl), 1.24 (t, J = 7 Hz, 3H, CH_3 of ethyl), 1.42-1.56 (m, 2H, H-1 of butyl), 3.42 (*s*, 3H, NCH_3), 4.05 (*s*, 1H, OH), 4.16 (q, J = 7 Hz, 2H, CH_2 of ethyl), 6.47 (*s*, 1H, olef H), 7.05 (dd, J = 7 and 2 Hz, 1H, H-8), 7.12 (dt, J = 7 and 2 Hz, 1H, H-6), 7.41 (dt, J = 7 and 2 Hz, 1H, H-7), 7.66 (dd, J = 7 and 2 Hz, 1H, H-5)
4c	3480, 2960, 2930, 2860, 1720, 1688, 1634, 1601, 1495, 1461, 1337, 1304, 1271, 1231, 1178, 1159, 1070, 1050, 1029, 883, 766, 752, 696	In deuteriochloroform (400 MHz): 0.83 (t, J = 7 Hz, 3H, CH_3 of butyl), 1.23 (m, 2H, H-3 of butyl), 1.29 (t, J = 7 Hz, 3H, CH_3 of ethyl), 1.37 (m, 2H, H-2 of 1206, butyl), 1.69 (m, 2H, H-1 of butyl), 4.06 (s, 1H, OH), 4.21 J = 7 Hz, (q, J = 7 Hz, 2H, CH_2 of ethyl), 6.45 (dd, J = 8 and 2 Hz, 1H, H-8), 6.57 (s, 1H, olef H), 7.09 (dd, J = 8 and 2 Hz, 1H, H-6), 7.22 (dd, J = 8 and 2 Hz, 1H, H-7), 7.25 (m, 2H, *o*-H of C_6H_5), 7.46 (m, 1H, *p*-H of C_6H_5), 7.53 (m, 2H, *m*-H of C_6H_5), 7.74 (dd, J = 8 and 2 Hz, 1H, 5-H) ^{13}C nmr (100 MHz, in deuteriochloroform): 13.9 q, 14.1 q, 22.5 t, 25.2 t, 38.2 t, 60.5 t, 116.2 d, 117.1 d, 121.7 s, 123.3 s, 128.5 d (2C, *o*-C of C_6H_5), 128.7 d, 130.0 d (2C, *m*-C of C_6H_5), 130.3 d, 130.4 d, 137.5 *s*, 138.9 *s*, 148.9 *s*, 166.1 s, 172.5 *s*
4d	3498, 3324, 1701, 1685, 1638, 1612, 1585, 1478, 1379, 1321, 1272, 1211, 1178, 1029, 878, 761, 712, 699, 688	1.11 (t, J = 7 Hz, 3H, CH_3), 2.68 and 2.83 (2d, J = 13 Hz, 2H, $ArCH_2$), 4.02 (q, J = 7 Hz, 2H, CH_2), 5.83 (*s*, 1H, olef H), 5.97 (s, 1H, OH), 6.93-7.24 (m, 7H, H-6, H-8 and C_6H_5), 7.37 (t, J = 8 Hz, 1H, H-7), 7.42 (d, J = 8 Hz, 1H, H-5), 10.58 (s, 1H, NH)
4e	3465, 1728, 1674, 1642, 1603, 1471, 1292, 1209, 1180, 1131, 1098, 1028, 758, 752, 699	1.09 (t, J = 7 Hz, 3H, CH_3), 2.65 and 2.82 (2d, J = 13 Hz, 2H, $ArCH_2$), 3.37 (s, 3H, NCH_3), 4.03 (q, J = 7 Hz, 2H, CH_2), 5.89 (s, 1H, OH), 6.15 (s, 1H, olef H), 6.88-7.32 (m, 7H, H-6, H-8 and C_6H_5), 7.46 (d, J = 8 Hz, 1H, H-7), 7.53 (d, J = 7 Hz, 1H, H-5). In deuteriochloroform: 1.23 (t, J = 7 Hz, 3H, CH_3), 2.78 and 2.88 (2d, J = 13 Hz, 2H, $ArCH_2$), 3.45 (s, 3H, NCH_3), 4.14 (q, J = 7 Hz, 2H, OCH_2), 4.16 (s, 1H, OH), 6.32 (*s*, 1H, olef H), 6.95-7.32 (m, 6H, H-6 and C_6H_5), 7.11 (d, 1H, H-8), 7.46 (dt, J = 7 and 2 Hz, 1H, H-7), 7.72 (dd, J = 7 and 2 Hz, 1H, H-5)
4f	3422, 1722, 1671, 1636, 1602, 1464, 1345, 1231, 1201, 1162, 1153, 764, 748, 705, 692	In deuteriochloroform: 1.24 (t, J = 7 Hz, 3H, CH_3), 2.93-3.12 (m, 2H, $ArCH_2$), 4.17 (q, J = 7 Hz, 2H, CH_2), 4.20 (s, 1H, OH), 6.41 (*s*, 1H, olef H), 6.55 (d, J = 7 Hz, 1H, H-8), 7.08-7.62 (m, 12H, H-6, H-7 and two C_6H_5), 7.79 (dd, J = 7 and 2 Hz, 1H, H-5)
4g	3420, 3090, 1712, 1689, 1625, 1586, 1485, 1450, 1397, 1363, 1354, 1247, 1210, 1184, 1170, 1150, 1110, 1082, 770, 760, 753, 703	1.19 (t, J = 7 Hz, 3H, CH_3), 4.12 (q, J = 7 Hz, 2H, CH_2), 6.52 (s, 1H, olef H), 6.63 (*s*, 1H, OH), 6.85 (d, J = 8 Hz, 1H, H-8), 6.87 (t, J = 8 Hz, 1H, H-6), 7.15-7.30 (m, 6H, H-7 and C_6H_5), 7.40 (d, J = 8 Hz, 1H, H-5), 10.80 (s, 1H, NH)
4h	3455, 1708, 1664, 1605, 1465, 1450, 1374, 1285, 1272, 1171, 1134, 1095, 1085, 1065, 1043, 1032, 1021, 779, 764, 705, 691, 651	1.20 (t, J = 7 Hz, 3H, CH_3), 3.43 (s, 3H, NCH_3), 4.15 (q, J = 7 Hz, 2H, CH_2), 6.53 (s, 1H, OH), 6.54 (s, 1H, olef H), 6.97 (t, J = 8 Hz, 1H, H-6), 7.12 (d, J = 8 Hz, 1H, H-8), 7.15-7.25 (m, 5H, C_6H_5), 7.27 (t, 1H, H-7), 7.40 (d, J = 8 Hz, 1H, H-5)
4i	3441, 1728, 1713, 1674, 1639, 1599, 1488, 1453, 1338, 1321, 1297, 1269, 1209, 1188, 1169, 1132, 1102, 1045, 1022, 985, 762, 750, 691	1.24 (t, J = 7 Hz, 3H, CH_3), 4.19 (q, J = 7 Hz, 2H, CH_2), 6.19 (d, J = 7 Hz, 1H, H-8), 6.73 (s, 1H, olef H), 6.77 (s, 1H, OH), 6.94 (t, J = 7 Hz, 1H, H-6), 7.12 (t, J = 7 Hz, 1H, H-7), 7.19-7.70 (m, 10H, two C_6H_5), 7.61 (d, J = 7 Hz, 1H, H-5)
5a	3200, 3150, 2925, 2861, 1765, 1752, 1693, 1635, 1605, 1582, 1474, 1357, 1320, 1228, 1138, 981, 846, 773	0.79 (t, J = 7 Hz, 3H, CH_3), 1.18 (br s, 4H , H-2 and H-3 of butyl), 1.67 and 2.01 (2m, 2H, H-1 of butyl), 6.52 (s, 1H, H-1), 7.11 (d, J = 7 Hz, 1H, H-6), 7.21 (t, J = 7 Hz, 1H, H-8), 7.53 (t, J = 7 Hz, 1H, H-7), 7.76 (d, J =7 Hz, 1H, H-9), 10.79 (s, 1H, NH) ^{13}C nmr: 15.5 (4-C of butyl), 23.4 (3-C of butyl), 26.1 (2-C of butyl), 38.8 (1-C of butyl), 88.0 (3a-C), 114.1 (1-C), 117.2, 118.1, 125.2, 129.1, 135.0, 139.1, 165.4, (9b-C), 168.7 (4-C), 172.9 (2-C)

Table 4 (continued)

Compound No.	IR (cm^{-1})	^{1}H-NMR δ (ppm)
5b	2936, 1741, 1682, 1644, 1599, 1467, 1358, 1328, 1282, 1232, 1044, 976, 928, 847, 771	0.77 (t, J = 7 Hz, 3H, CH_3), 1.14 (br s, 4H, H-2 and H-3 of butyl), 1.64 and 1.94 (2m, 2H, H-1 of butyl), 3.34 (s, 3H, NCH_3), 6.51 (s, 1H, H-1), 7.32 (d, J = 7 Hz, 1H, H-6), 7.37 (t, J = 7 Hz, 1H, H-8), 7.62 (t, J = 7 Hz, 1H, H-7), 7.76 (d, J = 7 Hz, 1H, H-9) In deuteriochloroform (500 MHz): 0.81 (t, J = 7 Hz, 3H, CH_3), 1.23 (m, 4H, H-2 and H-3 of butyl), 1.65 and 2.09 (2m, 2H, H-1 of butyl), 3.42 (s, 3H, NCH_3), 6.07 (s, 1H, H-1), 7.16 (d, J = 8 Hz, 1H, H-6), 7.24 (t, J = 7 Hz, 1H, H-8), 7.56 (t, J = 8 Hz, 1H, H-7), 7.58 (d, J = 8 Hz, 1H, H-9)
5c	1790, 1752, 1706, 1641, 1598, 1491, 1461, 1351, 1320, 1292, 1276, 1259, 1234, 1135, 1085, 940, 862, 775, 768, 739, 700	0.80 (t, J = 7 Hz, 3H, CH_3), 1.23 (br s, 4H, H-2 and H-3 of butyl), 1.80-1.95 and 2.05-2.25 (2m, 2H, H-1 of butyl), 6.35 (d, J = 8 Hz, 1H, H-6), 6.63 (s, 1H, H-1), 7.15-7.70 (m, 7H, H-7, H-8 and C_6H_5), 7.83 (d, J = 8 Hz, 1H, H-9)
5d	3288, 1812, 1771, 1752, 1700, 1682, 1634, 1608, 1479, 1452, 1357, 1333, 1300, 1269, 1229, 1152, 1118, 1084, 935, 843, 768, 702, 686, 671	3.04 and 3.37 (2d, J = 14 Hz, 2H, CH_2), 6.23 (s, 1H, H-1), 6.83-7.33 (m, 7H, H-6, H-8 and C_6H_5), 7.57 (t, J = 7 Hz, 1H, H-7), 7.65 (d, J = 7 Hz, 1H, H-9), 10.91 (s, 1H, NH)
5f	1772, 1758, 1709, 1640, 1599, 1494, 1485, 1465, 1330, 1328, 1281, 1265, 1236, 1110, 1082, 939, 928, 880, 844, 777, 730, 699, 640	In deuteriochloroform: 3.22 and 3.61 (2d, J = 14 Hz, 2H, CH_2), 5.88 (s, 1H, H-1), 6.52 (d, J = 8 Hz, 1H, H-6), 6.95-7.68 (m, 13H, H-7, H-8, H-9, and two C_6H_5)
5i	1764, 1703, 1638, 1600, 1492, 1461, 1450, 1345, 1292, 1279, 1208, 1168, 777, 723, 695	6.28 (d, J = 7 Hz, 1H; H-6), 6.91 (s, 1H, H-1), 7.20-7.70 (m, 12 H, H-7, H-8 and two C_6H_5), 7.91 (dt, J = 7 and 2 Hz, 1H, H-9)
6a	3240, 2950, 2920, 2855, 1681, 1628, 1582, 1476, 1372, 1340, 1230, 1180, 849, 769, 752, 678, 650	0.73 (t, J = 7 Hz, 3H, CH_3 of butyl), 1.13 (br s, 4H, H-2 and H-3 of butyl), 1.24 and 1.48 (2m, 2H, H-1 of butyl), 5.69 (s, 1H, OH), 6.24 (s, 1H, olef H), 6.90 (d, J = 7 Hz, 1H, H-8), 6.99 (t, J = 7 Hz, 1H, H-6), 7.30 (t, J = 7 Hz, 1H, H-7), 7.49 (d, J = 7 Hz, 1H, H-5), 10.43 (s, 1H, NH), 12.48 (br s, 1H, COOH)
6b	3400, 2940, 1685, 1675, 1661, 1631, 1600, 1460, 1413, 1368, 1340, 1298, 1255, 1235, 1220, 1184, 1132, 1105, 745, 681	0.72 (t, J = 7 Hz, 3H, CH_3 of butyl), 0.95-1.50 (m, 6H, three CH_2 of butyl), 3.32 (s, 3H, NCH_3), 5.79 (s, 1H , OH), 6.24 (s, 1H, olef H), 7.09 (t, J = 7 Hz, 1H, H-6), 7.19 (d, J = 7 Hz, 1H, H-8), 7.42 (t, J = 7 Hz, 1H, H-7), 7.50 (d, J = 7 Hz, 1H, H-5), 12.48 (br s, 1H, COOH)
6c	3446, 1723, 1629, 1599, 1565, 1449, 1408, 1376, 1250, 1211, 1155, 880, 770, 754, 710, 698	0.92 (t, 3H, CH_3), 1.36 (br s, 4H, H-2 and H-3 of butyl), 2.19 (m, 2H, H-1 of butyl), 6.19 (br s, 1H, OH), 6.60 (d, J = 7 Hz, 1H, H-8), 6.88 (s, 1H, olef H), 7.15-7.78 (m, 7H, H-6, H-7 and C_6H_5), 8.11 (d, J = 7 Hz, 1H, H-5), 12.82 (br s, 1H, COOH)
6d	3420, 3020, 1729, 1685, 1660, 1620, 1582, 1492, 1479, 1451, 1429, 1321, 1276, 1226, 1131, 1103, 860, 848, 759, 698, 671, 650	2.67 and 2.82 (2d, J = 13 Hz, 2H, $ArCH_2$), 5.94 (s, 1H, OH), 6.04 (s, 1H, olef H), 6.93-7.25 (m, 6H, H-8 and C_6H_5), 7.06 (t, J = 8 Hz, 1H, H-6), 7.36 (t, J = 8 Hz, 1H, H-7), 7.51 (d, J = 8 Hz, 1H, H-5), 10.65 (s, 1H, NH), 12.40 (br s, 1H, COOH)
6e	3365, 3200, 1699, 1655, 1632, 1596, 1465, 1455, 1425, 1392, 1375, 1293, 1233, 1204, 1175, 1130, 1097, 1058, 895, 848, 775, 758, 739, 698, 678, 628	2.63 and 2.79 (2d, J = 14 Hz, 2H, CH_2), 3.38 (s, 3H, NCH_3), 5.88 (s, 1H, OH), 6.08 (s, 1H, olef H), 6.87-7.54 (m, 8H, H-6, H-7, H-8 and C_6H_5), 7.49 (d, J = 7 Hz, 1H, H-5), 12.39 (br s, 1H, COOH)
6f	3220 - 3600br, 1720, 1628, 1598, 1567, 1495, 1450, 1381, 1201, 1110, 772, 765, 744, 695	3.47 and 3.58 (J = 13 Hz, 2d, 2H, $ArCH_2$), 6.36 (br s, 1H, OH), 6.58 (d, J = 8 Hz, 1H, H-8), 6.74 (s, 1H, olef H), 7.05-7.73 (m, 12H, H-6, H-7 and two C_6H_5), 8.13 (d, J = 8 Hz, 1H, H-5)
6g	3360, 1700, 1686, 1635, 1487, 1451, 1427, 1365, 1336, 1280, 1236, 1190, 1164, 1148, 1110, 1015, 1005, 981, 863, 765, 750, 700, 680, 648	6.45 (s, 1H, OH), 6.63 (s, 1H, olef H), 6.85 (d, J = 8 Hz, 1H, H-8), 6.89 (t, J = 8 Hz, 1H, H-6), 7.15-7.35 (m, 6H, H-7 and C_6H_5), 7.45 (d, J = 8 Hz, 1H, H-5), 10.75 (s, 1H, NH), 12.70 (br s, 1H, COOH)
6h	3505, 2800 - 3330 br, 1712, 1665, 1634, 1610, 1477, 1400, 1316, 1237, 1191, 1139, 1107, 860, 789, 771, 759, 706, 689, 639	3.42 (s, 3H, CH_3), 6.58 (s, 1H, OH), 6.64 (s, 1H, olef H), 6.97 (t, J = 8 Hz, 1H, H-6), 7.06-7.33 (m, 7H, H-7, H-8 and C_6H_5), 7.43 (d, J = 8 Hz, 1H, H-5), 12.66 (s, 1H, COOH)
6i	3405, 1705, 1622, 1592, 1564, 1535, 1488, 1447, 1375, 1347, 1278, 1240, 1140, 1091, 1062, 954, 871, 774, 751, 725, 712, 701, 692, 658	6.13 (s, 1H, olef H), 6.56 (d, J = 8 Hz, 1H, H-8), 7.17 (t, J = 8 Hz, 1H, H-6), 7.25-7.70 (m, 11H, H-7 and two C_6H_5), 8.04 (d, J = 8 Hz, 1H, H-5)

spot with characteristic light blue fluorescence corresponding to butenolides **5**, if they were exposured to air and sunlight for a long time, especially in the solution of organic solvents. It is described [11] that in the Wittig reaction of substituted salicylaldehydes with phosphorane **3** *E*-2-hydroxycinnamates and only small quantity of substituted coumarines were formed at lower reaction temperature. But, at higher reaction temperature and especially in the presence of basic solvents, isomerization takes place and the major product substituted is coumarine. Therefore, we verified that the isomerization of the product **4** to butenolide **5** takes place in the course of the reaction of **2** with **3**. The tlc analysis of the mixtures obtained by the heating of the esters **4** with 0.5 equivalent of phosphorane **3** and 0.5

equivalent of triphenylphosphane oxide at 160° for 3 hours showed that only non-isolable traces of the butenolides **5** were formed. Even after 8 hours of heating the quantity of the butenolide **5** in the reaction mixture was negligible. Results of these experiments showed that only very small quantities of the butenolides **5** can arise by the isomerization of the esters **4** under reaction conditions.

However, we cannot exclude the base catalyzed reesterification of the ylide **3** with the tertiary hydroxyl group of **2** that may proceed in a small extent during the Wittig reaction. This ester can cyclize itself to the butenolide **5**. We observed that the intramolecular cyclization of such phosphorane esters proceeds very easily. This hypothesis is supported by the fact that *N*-phenyl derivatives of **2**, in which the tertiary hydroxyl group is more acidic due to inductive effect of the phenyl group and, therefore, the formation of nucleophilic alcoholate anion is more likely to afford higher yields of butenolides **5**.

The hydrolyses of the esters **4** with ethanolic potassium hydroxide afforded the acids **6** in high yields and the formation of any other products, *e.g.* isomeric ones, was not observed. It is noteworthy that the crystalline adducts of the product with one molecule of benzene (determined from elemental analyses and nmr spectra) were obtained in the cases of acids **6a** and **6b** after their recrystallization; benzene was removed by drying at 110° for 2 hours.

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 421 spectrophotometer using samples in potassium bromide disks. The nmr spectra were recorded in hexadeuteriodimethyl sulfoxide (unless otherwise indicated) and with TMS as internal standard; the instruments used were a Varian XL 200 at 200 MHz and a Varian VXR-400 (400 MHz for ^{1}H, 100 MHz for ^{13}C). Column chromatography was carried out on silica gel Silpearl (Kavalier, Votice). The purity of substances was checked by thin-layer chromatography on Silufol UV 254 foils (Kavalier, Votice).

General Procedure for the Preparation of 3-Hydroxy-1,2,3,4-tetrahydroquinoline-2,4-diones **2a-f**.

To the solution of appropriate 4-hydroxy-2(1*H*)-quinolone **1a-f** (40 mmoles) in 0.5 *M* sodium hydroxide (380 ml), 40 ml of 30% peroxyacetic acid in acetic acid was added dropwise under stirring at room temperature for 30 minutes. After additional stirring at room temperature (30 minutes), the precipitated product was filtered with suction, disperged in 5% sodium bicarbonate solution (50 ml), filtered and washed with water until the filtrate was neutral. When the unreacted compound **1** was present in the product (according to tlc), it was removed by the extraction of the chloroform solution of the crude product with 0.05 *M* sodium hydroxide.

General Procedures for the Preparation of *E*-3-Hydroxy-4-ethoxycarbonylmethylene-1,2,3,4-tetrahydroquinolin-2-ones **4**.

Method A.

The mixture of the appropriate 3-hydroxy-1,2,3,4-tetrahydroquinoline-2,4-dione **2** (10 mmoles) and **3** (10 mmoles) was heated under vacuum at a bath temperature of 150-160° for 2-4 hours. After cooling, the glass mixture of the product and triphenylphosphaneoxide was crystallized (only in several cases) or column chromatographed.

Method B.

The suspension of the corresponding compound **2** (10 mmoles) and **3** (10 mmoles) in xylene (30 ml) was refluxed for 2-4 hours. During 30 minutes the suspension becomes clear. After cooling, the product crystallizes from the reaction mixture in several cases. In other cases, the solution was evaporated to dryness *in vacuo* and the residue was crystallized or column chromatographed.

Substituted 2,3a,4,5-Tetrahydrofuro[2,3-*c*]quinoline-2,4-diones **5**.

These compounds were obtained by column chromatography of the reaction mixtures from the reaction of **2** with **3** and/or of mother liquors after crystallization of **4**.

General Procedure for the Preparation of the *E*-4-Carboxymethylene-3-hydroxy-1,2,3,4-tetrahydroquinolin-2-ones **6**.

The solution of the appropriate ester **4** (5 mmoles) in ethanolic (15 ml) potassium hydroxide (20 mmoles) containing 2 ml of water was refluxed for 3 hours. After evaporation to dryness *in vacuo*, the residue was dissolved in water (50 ml) and acidified with concentrated hydrochloric acid. The crystals which separated were filtered with suction and recrystallized.

Acknowledgments.

This study was supported by the Grant Agency of the Czech Republic (Grant No. 104/94/0104). The authors are indebted to Dr. P. Sedmera (Institute of Microbiology, Academy of Sciences of the Czech Republic) for measuring the ^{13}C nmr spectrum of compound **4c** and for fruitful discussions.

REFERENCES AND NOTES

[1] A. Closse, W. Haefliger, and D. Hauser, *J. Med. Chem.*, **24**, 1465 (1981).

[2] K. Faber, H. Stückler, and T. Kappe, *J. Heterocyclic Chem.*, **21**, 1177 (1984).

[3] P. Garner and S. Ramakanth, *J. Org. Chem.*, **52**, 2929 (1987) and references therein.

[4] S. Kitamura, K. Hashizume, T. Iida, E. Miyashita, K. Shirahata and H. Kase, *J. Antibiot.*, **39**, 1160 (1986).

[5] R. Laschober and W. Stadlbauer, *Liebigs Ann. Chem.*, 1083 (1990).

[6] W. Stadlbauer and T. Kappe, *Z. Naturforsch.*, **37b**, 1196 (1982).

[7] W. Stadlbauer, H. Lutschounig, G. Schindler, T. Witoszynskyj and T. Kappe, *J. Heterocyclic Chem.*, **29**, 1535 (1992).

[8] T. Kappe, E. Ziegler, E. Reichel-Lender and P. Fritz, *Monatsh. Chem.*, **100**, 951 (1969).

[9] K. Faber, H. Steininger and T. Kappe, *J. Heterocyclic Chem.*, **22**, 1081 (1985).

[10] H. O. House and G. H. Rasmusson, *J. Org. Chem.*, **26**, 4278 (1961).

[11] T. Harayama, K. Katsuno, H. Nishioka, M. Fujii, Y. Nishita, H. Ishii and Y. Kaneko, *Heterocycles*, **39**, 613 (1994).